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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,137	02/17/2004	Tamara Minko	744-53	2173

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
12/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,137	MINKO ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,10,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5, 10 and 15-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 10/16/2007 in response to the previous Non-Final Office Action (4/18/2007) is acknowledged and has been entered.

Claims 5, 10 and 15-16 are currently pending and under consideration.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 10 and 15-16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Trouet et al. (WO 01/91798, 2001, *of record*) in view of Chatzistamou et al. (Clinical Cancer Research 2000; 6: 4158-4165, *of record*).

Trouet et al. teach a prodrug for treating cancer comprising a biologically active entity linked to a masking moiety via a linking moiety (abstract). With regards to the biologically active entity, the WO document teaches (page 60, claim 51 of the WO document) that the biologically active entity includes, but is not limited to, BH3 peptides and anticancer agents such as anthracyclines, doxorubicin and camptothecins. With regards to the linking group, Trouet et al. teach (page 2, lines 17-23) that the linking moieties are preferably peptides having the amino acid sequence of $(Leu)_y(Ala\text{-}Leu)_xAla\text{-}Leu$ and $(Leu)_y(Ala\text{-}Leu)_xAla\text{-}Phe$, where y is 0 or 1 and x is 1, 2, or 3. With regards to the masking moiety, the WO document teaches (page 5, lines 21-33, page 15, lines 16-35 and page 32, lines 14 +) that the masking moiety may have biological activity such that prodrug is a dual prodrug and further, comprise large molecular weight biologically inert molecules such as PEG or HPMA. Trout et al. further teach (page 6, lines 18-24) a method of treating cancer comprising administering the prodrug to an animal in an effective amount to shrink or eradicate the tumor. Furthermore, the WO document teaches (page 35, lines 24+) a method of making the prodrug

comprising condensing the masking moiety and biological entity with the linking moiety. Although Trouet et al. does not specifically teach that the linking moiety is a scaffold, the claimed limitation does not appear to result in a manipulative difference between the prior art because independent claim 10 and 16 recite that the scaffold is a peptide.

Trouet et al. do not explicitly teach that the prodrug further comprises LHRH.

Chatzistamou et al. teach an effective treatment of metastatic MDA-MB-435 human estrogen breast carcinomas which utilizes LH-RH analogues as targeted carriers for chemotherapeutics agents such as doxorubicin (Title and Abstract). Specifically, the references teaches that targeted chemotherapy is based on the concept of linking cytotoxic radicals to a carrier, which is able to recognize cancer cells, wherein selective accumulation of the chemotherapeutic agent can be achieved in the tumor while sparing the healthy tissues from exposure (page 4158, 2nd column, 2nd full paragraph). Moreover, Chatzistamou et al. teaches that the LH-RH analogues specifically target LH-RH receptors present on a variety of human tumors (page 4158, 2nd column, 3rd full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the reference so as to modify the dual prodrug taught by Trouet et al. to include LHRH in view of the teachings of Chatzistamou et al.. One would have been motivated to do so because Chatzistamou et al. teaches that the targeted chemotherapy is based on the concept that by linking cytotoxic radicals to a carrier, which is able to recognize cancer cells, a selective accumulation of the chemotherapeutic agent can be achieved in the tumor while sparing the healthy tissues from exposure. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the dual prodrug taught by Trouet et al. to include LHRH in view of the teachings of Chatzistamou et al, one would achieve a drug delivery complex which specifically targets tumors having LH-RH receptors and treating said tumors.

In response to this rejection, Applicants assert that Trouet is directed to a prodrug compound for inhibition of the growth of tumors, wherein its novel prodrug requires three specific components: a masking moiety such as PEG, a linking moiety, and a biologically active entity such as anticancer agents and BH3 peptide. In particular, Applicants assert that the Trouet disclosure emphasizes the novelty and importance of its "linking moiety" which is defined as a molecular moiety that "links a biologically active entity to a masking moiety and is susceptible to specific,

selective cleavage at or near a tumor or target cell (page 9, lines 16-18). Moreover, Applicants contend that according to Trouet, when the prodrug compound is in the presence of such target cell factors (such as proteases or peptidases), the linking moiety is cleaved, separating the masking moiety and the biologically active entity, wherein the biologically active entity exerts its activity on the target cells (page 11, lines 8-33). Thus, Applicants assert that the linking moiety is critical to Trouet's prodrug compound for controlling the selectivity of the compound. In contrast, Applicants assert that Chatzistamou discloses the use of LHRH linked to doxorubicin to form a cytotoid analog, which is targeted to LHRH recepts, but is silent on the use of poly(ethylene glycol) in combination with both an anticancer agent as well as BH3. Therefore, Applicants contend that one following the teachings of Trouet would not be motivated to incorporate Chatzistamou's LHRH, in view of the selectivity of the linking moiety of Trouet because as explained at length by Trouet, the allegedly novel feature of Trouet is the inclusion of the linking moiety which allows the biologically active agent to stay inert until it is cleaved from the masking moiety which will only occur in the presence of a selected tumor or target cell. In other words, Applicants contend that the addition of an LHRH carrier would be duplicative and unnecessary in light of the selectivity of the linking moiety. Applicants further assert that even if one was to consider combining the compound of Trouet with the LHRH of Chatzistamou, one skilled in the art would realize that there would likely be an issue of steric hindrance between the components which would likely decrease the activity of each component.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants assertions with respect to the teachings of Trouet and Chatzistamou, the Examiner acknowledges and agrees with Applicants short synopsis of what Trouet and Chatzistamou teach. However, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). There is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v.

Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, it is well known to one of ordinary skill in the art at the time of the invetion, as taught by Chatxistamou, that LHRH is used as a targeting carrier for chemotherapeutic agents, wherein a cytotoxic agent is linked to a carrier, which is able to recognize cancer cells, wherein selective accumulation of the chemotherapeutic agent can be achieved in the tumor while sparing the healthy tissues from exposure. Thus, while the Examiner does not dispute Applicants assertion that the novelty of Trouets' prodrug lies in the peptide linking moiety, e.g., the cleavage of the prodrug to form the biologically active compound by intracellular proteases or peptidases at the target cell, the Examiner recognizes that this does not appear to negate one of skill in the art from targeting Trouets's prodrug to tumor cells expressing an LHRH receptor. In other words, it appears that Applicants are asserting that a prodrug cannot be targeted via a targeted carrier. However, the Examiner recognizes that the concept of targeting prodrugs via a targeted carrier are well known in the art. See for example, US Patent 6,428,788, which teaches a chimeric molecule composed of a targeting molecule which specifically binds to a receptor on a target cell and an effector molecule such as a prodrug (lines 20-39). Lastly, regarding Applicants position that those of skill in the art would recognize that there would likely be steric hindrance between the components in combined, the Examiner acknowledges Applicants assertions. However, the Examiner recognizes that Applicants have not provided any evidence to support such an assertion. As such, this argument has not been considered.

Therefore, NO claim is allowed

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

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